UNITED STATES PATENT AND TRADEMARK OFFICE

C1C

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,999	10/28/2003	Ilia Davydov	2528-10	4116

23117 7590 06/20/2005

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
DESAI, ANAND U	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,999	DAVYDOV ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-8,10,12,15-17,35-47,55 and 57-63* is/are pending in the application.

4a) Of the above claim(s) *5-8,10,12,15,16,35-47 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,17 and 57-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050216*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to Amendment filed on February 16, 2005. Claims 25, and 48-53 have been cancelled. New claims 57-63 have been added. Claims 5-8, 10, 12, 15, 16, 35-47, and 55 have been previously withdrawn. Claims 3, 4, 17, and 57-63 are currently pending and are under examination.

Withdrawal of Rejections

2. The rejection of claim 17 under 35 U.S.C. 112, 2nd paragraph as being indefinite is withdrawn based on Applicants amendment.

3. The rejection of claims 3, 4, and 17 under 35 U.S.C. 102(b) as being anticipated by Maeda, I. et al. (FEBS Letter 494: 181-185 (2001)) is withdrawn based on Applicants amendment.

4. The rejection of claims 3, 4, and 17 under 35 U.S.C. 102(b) as being anticipated by Elsasser, S. et al. (Molecular Biology of the Cell 10: 3263-3277 (1999)) is withdrawn based on Applicants amendment.

5. The rejection of claims 3, 4, and 17 under 35 U.S.C. 102(b) as being anticipated by Morishima-Kawashima, M. et al. (Neuron 10(6): 1151-1160 (1993)) is withdrawn based on Applicants amendment.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on February 16, 2005 is being considered by the examiner. The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date

of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609 subsection III. C(1).

Maintenance of Rejections

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 3, 4, 17, and 57-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. The claims are directed to a polypeptide having 60% sequence "similarity". It is not clear what is encompassed by the word, "similarity?" Suggest, 60% sequence identity.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 3, 4, 17, and 57-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for an isolated complex comprising at least one ubiquitin and a protein selected from the group consisting of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, HSPC144, tau, Cullin 3, and CDC6, formed via the N-end rule mechanism, does not reasonably provide enablement for isolated complexes comprising **derivatives of ubiquitin** with **fragments**

and derivatives of proteins selected from the group consisting of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, HSPC144, tau, Cullin 3, and CDC6, formed via the N-end rule mechanism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

1.) The nature of the invention: the invention is drawn to an isolated complex comprising at least one ubiquitin or a derivative thereof, and a protein, wherein said protein is selected from the group consisting of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, HSPC144, tau, Cullin 3, and CDC6, and fragments and derivatives thereof, wherein said fragments and derivatives thereof comprise polypeptides of at least 10 amino acids having at least 60% sequence similarity to sequences within their corresponding proteins, and said complex is formed via N-end rule ubiquitylation.

2.) The breadth of the claims: the claims are extremely broad in that a very large number of constituents could be encompassed by ubiquitin derivatives, and fragments and derivatives of proteins selected from the group of proteins recited. Sixty percent of 10 is 6 so the fragments of ubiquitin alone comprise 70 molecules.

3.) The predictability or unpredictability of the art: there is unpredictability in the art with regard to the tertiary structure required for the interaction of substrate with the cognate E3 ubiquitin-protein ligase enzymes. Experiments have shown that optimal binding of substrate with E3 ubiquitin ligase may require a specific conformation (see Pickart, C. M. Annu. Rev.

Biochem. 70: 503-533 (2001), particularly pp. 513-55, Ubiquitin-Protein Ligases (E3s)). Thus, there is no way to predict whether any of the fragments or derivatives will interact with E3 ubiquitin ligase.

4.) & 5.) The amount of direction or guidance presented:/The presence or absence of working examples: the examples of full-length RGS4, tau, aprataxin, synaptotagmin-like protein 2, High Mobility Group Chromosomal Protein 17, CDC 6, HSPC144, PIN2 Interacting Protein 1, HMGN3, and CIR proteins as substrates for N-end rule ubiquitylation substrates do not in any way suggest that fragments and derivatives of the respective proteins, or a derivative of ubiquitin would have the conformations structures necessary to be considered substrates for the E3 ubiquitin ligases used in the ubiquitination pathway. The specification provides guidance with respect to the full-length proteins discussed in the working examples but provides no guidance whatsoever in selecting which fragments and derivatives might have the needed conformations. Further, no guidance is provided as to how to determine which fragments and derivatives might work.

6.) The quantity of experimentation necessary: there is a large quantity of experimentation necessary to determine which substrates, fragments and derivates, are capable of forming the requisite tertiary structure to form substrate-E3 ligase complexes during the process of forming an ubiquitinated protein complex, because of the limited understanding of particular E3 ubiquitin ligase active sites which are required during enzyme-substrate interaction (see Pickar, C.M. page 513-528).

7.) The state of the prior art: the prior art has shown that ubiquitination usually results in the formation of a bond between the carboxy terminus of ubiquitin (Gly76) and the ε-amino

group of a substrate lysine residue. This reaction requires the sequential actions of three enzymes: (a) an activating enzyme (E1) that forms a thiol ester with the carboxyl group of Gly76, thereby activating the carboxy terminus of ubiquitin for nucleophilic attack; (b) a conjugating enzyme (E2) that transiently carries the activated ubiquitin molecule as a thiol ester; and (c) a ligase (E3) that transfers the activated ubiquitin from the E2 to the substrate (or ubiquitin) lysine residue. The recognition of substrates for ubiquitination is governed by the presence and accessibility of structural motifs in the substrate, known as ubiquitination signals that are recognized by cognate E3s. Thus, E3s are the central determinants of specificity in ubiquitination (see Pickar, C.M., Introduction section).

8.) Level of skill in the art: the level of skill in this art is high, at least that of a doctoral scientist with several years of experience in the art.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

11. Claims 3, 4, 17, and 57-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 3, 4, 17, and 57-63 are drawn to a complex or composition comprising a derivative of ubiquitin, and a fragment or derivative of a protein, wherein said

fragment or derivative comprise polypeptides of at least 10 amino acids having at least 60% sequence similarity to sequences within the corresponding proteins selected from the group consisting of aprataxin, tau, SLP, HMG17, PinX1, CIR, Cullin 3, HMGN3, HSPC144, and CDC6. The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

Just as the claims at issue in *UC v. Lilly* defined the invention by the function of the claimed DNA (encoding insulin), the instant claims define the claimed products only by their functional properties. The court held this sort of functional definition insufficient. "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A

definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." *UC v. Lilly*, at *24-*25, thus the above claims lack adequate written description. The specification does not clearly describe the derivatives of ubiquitin, or the fragments or derivatives of a protein selected from the group consisting of aprataxin, tau, SLP, HMG17, PinX1, CIR, Cullin 3, HMGN3, HSPC144, and CDC6 that would encompass the isolated complex or composition. Which 10 amino acids having 6 of 10 amino acids identical with a selected protein from the Markush group will have the same biological function as the full-length protein? The specification does not describe the structure that is which amino acids in the polypeptide can be altered without affecting the function of a specific polypeptide? For one to be in possession of the claimed invention, the inventors would have to know the functional consequences of structural alterations.

Response to Remarks

Applicants urge that claims 3, 4, and 17 are clear in view of their disclosure in the specification, and that a skilled artisan would readily recognize what Applicant regards as their invention. Applicant's arguments filed February 16, 2005 have been fully considered but they are not persuasive. Based on the description of pages 41-44 and the claims, a fragment or derivative can be any peptide of at least 10 amino acids having at least 60% sequence similarity to sequences within their corresponding proteins. It is not certain from the amended claim that the fragment and derivatives have an exposed destabilized Type I or Type II N-terminal amino acid consisting of amino acids selected from Arg, Lys, His, Phe, Leu, Trp, Tyr, and Ile. It is not evident from the claims that fragments and derivatives with 60% sequence similarity would have

the same biological function of the full-length polypeptide such that would be readily recognized by a person having ordinary skill in the art. Furthermore, it is not evident from the claims that ubiquitin is covalently attached to the protein, fragments, and derivatives, or is merely a constituent of the isolated complex. A broadest reasonable interpretation of the claims of an isolated complex comprising at least one ubiquitin and a protein would not require the ubiquitin be bound to the protein. Suggest clarifying the claim to describe the 10 amino acids with exposed destabilized N-terminal amino acids that retain biological function of the protein selected from the group consisting of aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, and HSPC144 covalently bound by ubiquitin. Applicant is certainly aware that "During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). See MPEP 2111. Therefore, the amended claims have not clearly described the fragments and derivatives of the proteins.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 3, 4 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Kleinschmidt et al. (Nucleic Acid Research 9(11): 2423-2431 (1981)).

Kleinschmidt et al. disclose an isolated complex comprising at least one ubiquitin and a protein, wherein the protein is HMG17. Kleinschmidt et al. assayed the binding of HMG17 with ubiquitinated histone H2A by gel electrophoresis. Pure HMG17 was mixed with native or reconstituted core particles containg an ubiquinated H2A histone (uH2A); the samples were electrophoresed on a 3.5% polyacrylamide, 0.5% agarose gel. The gels were stained using a label, 2 μg/ml of ethidium bromide (see Materials and Methods, Complexing of HMG Proteins to Native and Reconstituted Core Particles, page 2426). The ethidium bromide stained gel reveals the reduction in mobility of ubiquitinated H2A histone containing core particles upon the binding of HMG17 (see Results section, page 2428-2430, Association of HMG Proteins 14 and 17 with Core Particles Containing Two uH2A molecules, and Figure 4, particularly lanes 2a, and 3a, current application, claims 3, 4, and 17). A broadest reasonable interpretation of the claims of an isolated complex comprising at least one ubiquitin and a protein consisting of HMG17 would be encompassed by the reference of Kleinschmidt et al. Applicant is also referred to MPEP 2113, which states, "If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)."

14. Claims 57, 58, 59, 62, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Maeda, I. et al. (FEBS Letters 494: 181-185 (2001)). Maeda, I. et al. disclose an isolated complex comprising at least one ubiquitin and a protein, wherein the protein is Cullin 3. 293T cells were co-transformed with myc-tagged Cullin 3, and a small RING finger protein, ROC1

(subunit member of E3-Ubiquitin ligase). ROC1-cullin 3 immunoprecipitated protein were immobilized on protein A-agarose beads and added to an *in vitro* ubiquitination assay in the presence of ubiquitin conjugating enzymes, E1, E2, and unlabeled bovine ubiquitin. The complex was immobilized and labeled with a mouse monoclonal c-myc antibody. Figure 4 shows the ubiquitination of Cullin 3 (see pp. 184, Figure 4, lane 4, middle panel, current application, claims 3, 4, and 17).

13. Claims 57, 58, 59, 62, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Elsasser, S. et al. (Molecular Biology of the Cell 10: 3263-3277 (1999)). Elsasser, S. et al. disclose an isolated complex comprising at least one ubiquitin and a protein, wherein the protein is CDC6. In vitro translated CDC6 substrate was mixed in an ubiquitination assay comprising ubiquitin enzymes (including CDC43), bovine ubiquitin, and ATP. The CDC6-ubiquitin complex was immobilized on a nitrocellulose membrane and labeled with an anti-Myc antibody. The immunoblotted composition identified CDC6 protein that was ubiquitinated (see pp. 3270, figure 4, lane 8, current application, claims 3, 4, and 17).

14. Claims 57, 58, 59, 62, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Morishima-Kawashima, M. et al. (Neuron 10(6): 1151-1160 (1993)). Morishima-Kawashima, M. et al. disclose an isolated complex comprising at least one ubiquitin and a protein, wherein the protein is tau. Morishima-Kawashima, M. et al. purified a Sarkosyl-insoluble fraction of proteins from Alzheimer's disease (AD) brain tissue. The purified fractions were run on a SDS-PAGE and immunoblotted. The tau-ubiquitin complex was immobilized on an immunoblot, and

the composition was labeled with an antibody. The antibody identified ubiquitinated tau protein (see last sentence of Abstract, Figure 1, Panels A-D, Experimental Procedures section titled Purification of the PHF Smear, and Antibodies and Immunoblotting, and First sentence of Discussion, current application, claims 3, 4, and 17).

Response to Remarks

Claims 3, 4, and 17 were previously rejected under 102(b) based on Maeda, I. et al. (FEBS Letters 494: 181-185 (2001)), Elsasser, S. et al. (Molecular Biology of the Cell 10: 3263-3277 (1999)), and Morishima-Kawashima, M. et al. (Neuron 10(6): 1151-1160 (1993)). Applicants traverse the rejections. Applicants contend the references do not teach the claimed subject matter. Applicant is referred to the response to the 112, 1st written description rejection as it relates to the broadest reasonable interpretation of pending claims. Applicant is also referred to MPEP 2113, which states, "If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)." The claims are not interpreted to read exclusively on an isolated complex wherein the ubiquitin is covalently attached to the proteins selected from Cullin 3, CDC6, and tau, rather the isolated complex merely comprises at least one ubiquitin along with the selected protein. As the amended claims 57, 58, 59, 62, and 63 are directed to an isolated complex comprising at least one ubiquitin or a derivative thereof, and a protein; wherein said protein is selected from the group consisting of tau, Cullin 3, CDC6, and fragments and derivatives thereof, proteins. The references were applied to claims 3, 4, and 17 because of these proteins, Cullin,

CDC6, and tau. The references are directed to complexes comprising at least one ubiquitin and the proteins selected from Cullin 3, CDC6, and tau. Therefore, claims 57, 58, 59, 62, and 63 are drawn to an isolated complex comprising at least one ubiquitin and a protein.

Conclusion

15. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 10, 2005

ROBERT A. WAX
PRIMARY EXAMINER
Art Unit 1653